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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/811,130	DEVARAJAN ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,9-11,28,30-40 and 46-59* is/are pending in the application.

4a) Of the above claim(s) *57 and 58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,9-11,28,30-40,46-56 and 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/13/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Newly submitted claims 57-58 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

The method for *detecting the development of acute renal failure secondary to an acute renal tubular cell injury* is directed to process that is related but patentably distinct than the methods of *detecting renal tubular cell injury* originally elected for consideration. The elected methods relate to detection, i.e. diagnosis of renal tubular cell injury and are performed on subjects suspected of having this injury (see for example step (a) of claim 1). By contrast, the methods of claims 57-58 involve subjects already known to have acute renal tubular cell injury (see step (a) of claim 57). As such, the newly presented claims involve a different, non-overlapping patient population and differ in function and in effect: claims 57-58 have the purpose and result of detecting development of ARF in patients known to have renal tubular cell injury, while the elected invention has the purpose and effect of detecting renal tubular cell injury in patients suspected (but not yet known) to have such an injury.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 57-58 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Status of the Claims

2. Applicant's amendment, filed 11/13/07, is acknowledged and has been entered. Claims 1, 11, 28, 30, 32-40, and 46 were amended. Claims 6, 8, 24, 26-27, and 41-45 were canceled. New claims 47-59 have been added, of which claims 57-58 have been withdrawn from examination as discussed above. Accordingly, claims 1-5, 9-11, 28, 30-40, and 46-59 are pending in the application, with claims 57-58 currently withdrawn. Claims 1-5, 9-11, 28, 30-40, 46-56, and 59 are subject to examination below.

Information Disclosure Statement

3. Applicant's Information Disclosure Statement filed 11/13/07 have been received and entered into the application. The references therein have been considered by the examiner as indicated on the attached form PTO-1449.

Objections/Rejections Withdrawn

4. The objections to the claims as set forth in the prior Office action are withdrawn in response to Applicant's persuasive arguments (Reply, page 24).

5. The objections to the specification not reiterated below have been withdrawn in light of Applicant's amendments thereto.

6. The rejections under § 112, 1st paragraph (new matter) not reiterated below have been withdrawn.

7. The rejections under § 112, 1st paragraph (scope of enablement) have been withdrawn in response to Applicant's amendments to claim 30.

8. The rejections under § 112, 2nd paragraph not reiterated below have been withdrawn in light of Applicant's amendments.

9. The Declaration under 37 CFR 1.132 filed 11/13/07 by inventors Devarajan and Barasch is sufficient to overcome the rejections of claims 1-2, 28, 30-37, 39-40, and 46 under § 102(a) based upon the Mishra et al. reference.

10. The rejections of claims 1 and 46 are rejected under § 102(b) as being anticipated by Venge et al. are withdrawn in response to Applicant's amendments thereto.

11. The provisional double patenting rejections over copending Application No. 11/374,285 are withdrawn in response to Applicant's persuasive arguments (Reply, page 44).

Priority

12. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(3) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/458,143, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

Provisional application No. 60/458,143 discloses methods for detecting *ischemic* renal injury, while the instant claims encompass both ischemic renal injury and nephrotoxic injury (see for example the preamble of claim 1). One skilled in the art would not envisage possession of methods of detecting all types of renal tubular cell injury (e.g., nephrotoxic injury) based on the disclosure of the prior-filed application relating only to ischemic types of injury. Furthermore, the provisional applications fail to disclose determination of *acute* nephrotoxic injury as instantly claimed.

Accordingly, the instant claims are not entitled to the benefit of the filing date of Application No. 60/458,143.

Specification

13. The disclosure is objected to because of the following informalities:

14. The use of trademarks (SuperScript™, Microcon™, GenePix™, Triton™) has been noted in this application. They should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 37 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

17. Claim 37 (added by Applicant's amendment of 3/12/07) recites "coronary bypass surgery". This term could not be found in the specification.

In addition, claim 37 recites a method in which NGAL is detected in urine samples obtained within specified periods of time in relation to an event that causes renal tubular cell injury (see claims 35-36), where the event may be "sepsis" or "dehydration".

The specification discloses kidney transplantation, cardiac surgery, stroke, trauma, sepsis, and dehydration at paragraph 38. However, this is in reference to **patients** who are at risk of developing acute renal failure. In other words, the disclosure conveys that the method could be used to diagnose acute renal failure in patients with sepsis or dehydration. There is no mention of these conditions being "events" or of urine samples being taken in reference to same. Although stroke and trauma might reasonably considered "events", it is not clear how the disease processes

of sepsis and dehydration could be considered "events" (see rejection under § 112, 2nd paragraph below).

Further, there is no description of such a method in which a urine sample is obtained *within 30 minutes of sepsis*, for example.

Paragraph 44 describes sampling intervals, i.e. every 24 hours, every 4 hours, or every 30 minutes. However, such disclosure does not adequately support the instant claims since there is no mention of a point of reference in this context. The noted passage simply refers to the spacing between when samples are collected, but does not describe sampling in relation to times after an event that causes a subject to have or be prone to developing renal tubular cell injury.

18. Claim 40 (added by Applicant's amendment of 3/12/07 and as amended in the instant Reply) recites a method wherein the NGAL level is "contrasted with a urinary NGAL level that distinguishes a mammalian subject that has an acute renal tubular cell injury from a mammalian subject that does not have an acute renal tubular cell injury". Support could not be found for the noted limitation in the specification or claims as originally filed. Applicant's reply refers to Examples 4-6 and Figures 9-16 (Reply, page 11). However, the noted passages refer to specific, detailed experiments and do not provide blaze marks or direction to the instantly claimed limitation.

The specification does not clearly disclose urinary NGAL levels "that distinguish a mammalian subject that has a renal tubular cell injury from a mammalian subject that does not have a renal tubular cell injury" (such as threshold levels) as such, or provide examples of what such levels would be. The specification does not introduce the concept of levels that distinguish

disease vs. controls as currently invoked by the claim. One skilled in the art cannot envisage possession of methods of comparing urinary NGAL levels to such distinguishing levels in the absence of any clear mention or indication of what values would be considered to distinguish the healthy and disease populations.

For example, claim 40 invokes threshold values that would distinguish any **acute** renal tubular cell injury. Applicant's instant Reply argues support for the claim at [0100]. However, the noted passage refers only to the results of an experiment involving patients with *cadaveric kidney transplant rejection* who had levels greater than 100 ng/ml. However, the instant claims would encompass any level that would distinguish any acute renal injury. One skilled in the art cannot envisage, based on the disclosure of levels greater than 100 ng/ml observed in cadaveric kidney transplant rejection, what other levels of NGAL might distinguish disease vs. healthy populations in other acute renal injury conditions.

19. Claims 1-5, 9-11, 30-40, 46-56, and 59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods in which the *level* of NGAL is correlated with the presence of renal tubular cell injury, does not reasonably provide enablement for methods in which the mere *presence* is correlate with the presence of injury. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Independent claim 30 as instantly amended and new claim 59 recite the step of "**correlating the presence of NGAL...to the presence of the acute renal tubular cell injury**" (see steps (b)).

Claims 1 and 46 as instantly amended conclude with the step of "correlating the detected antibody-NGAL complex to the presence of the acute renal tubular cell injury". This would encompass correlating either the simple presence of antibody-NGAL complex with the presence of injury (as in claims 30 and 59), as well as correlating the level of complex with the presence of injury (as in claim 28).

Therefore, the claims encompass methods in which the mere presence of NGAL (i.e., in any amount) would indicate the presence of acute renal tubular cell injury.

However, data reported in the specification only support the use of *elevated levels* of NGAL as an indication of the presence of disease. It is known that disease-free subjects possess detectable levels of urinary NGAL. See Suzuki et al. ("Neutrophil gelatinase-associated lipocalin as a biomarker of disease activity in pediatric lupus nephritis" Pediatr Nephrol (2008) 23:403–412), which teaches that healthy controls had detectable levels of NGAL (page 406, "Healthy controls", in particular the value reported for UNGAL (urinary NGAL)).

Therefore, the specification fails to teach the skilled artisan how to determine the presence of acute renal tubular cell injury based on the mere *presence* of NGAL in a subject's urine, given that even healthy subjects without injury would possess NGAL in urine.

20. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

21. Claims 37 and 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

22. Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The terms "sepsis" and "dehydration" in claim 37 are used by the claim to refer to examples of "events" while the accepted meanings are "severe illness caused by overwhelming infection of the bloodstream by toxin-producing bacteria" and "an abnormal depletion of body fluids", respectively. The terms are indefinite because the specification does not clearly redefine the term.

The specification discloses kidney transplantation, cardiac surgery, stroke, trauma, sepsis, and dehydration at paragraph 38. However, this is in reference to **patients** who are at risk of developing acute renal failure. In other words, the disclosure conveys that the method could be used to diagnose acute renal failure in patients with sepsis or dehydration. There is no mention of these conditions being "events" and it is not clear how they could be considered to represent specific "events" or points in time in relation to which urine samples are taken. Would this refer to the time of diagnosis? To the time at which sepsis or dehydration becomes clinically evident? Since the specification fails to make clear how sepsis and dehydration could be considered "events" in time, in relation to which urine samples are taken, the claims are indefinite.

23. Claim 40 recites that the NGAL level is contrasted with "a urinary NGAL level that distinguishes a mammalian subject that has an acute renal tubular cell injury from a mammalian

subject that does not have an acute renal tubular cell injury". However, the metes and bounds of the claim are unclear because the specification does not define or clearly exemplify what value or values of NGAL levels would be considered to distinguish normal vs. disease subjects (see also new matter rejection above). Consequently, one skilled in the art would not know based on the specification whether a particular NGAL level would fall within the scope of the claim or not.

Claim Rejections - 35 USC § 103

24. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

25. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

26. Claims 5, 30, 32-33, 50, and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Matthaeus et al. ("Acute Ischemic Renal Failure Induces Expression of Neutrophil Gelatinase-Associated Lipocalin and Matrix Metalloproteinase-9 in Damaged Tubuli" *Kidney*

Blood Press Res (2001), Vol. 24, page 342, abstract No. P268; hereafter, "Matthaeus 1") or Matthaeus et al. ("Co-Regulation of Neutrophil Gelatinase-Associated Lipocalin and Matrix Metalloproteinase-9 in the Postischemic Rat Kidney" *J. Am Soc Nephrol* Vol. 12, September 2001, Pathophysiology of Renal Disease, pp. 787A; A4112, SUI-0348 (PS), Applicant's IDS of 11/13/07; hereafter, "Matthaeus 2" in view of Gold et al. (US 6,242,246 B1), Ramsden et al. (US 4,640,909), Blaser et al. ("A sandwich enzyme immunoassay for the determination of neutrophil lipocalin in body fluids" Clin Chim Acta. 1995 Mar 31;235(2):137-45, Applicant's IDS of 7/24/06), and Moses et al. (US 7,153,660 B2), or in the alternative over either Matthaeus 1 or Matthaeus 2 and Ohlsson et al. ("Increased circulating levels of proteinase 3 in patients with anti-neutrophilic cytoplasmic autoantibodies-associated systemic vasculitis in remission" Clin Exp Immunol. (available online February 28, 2003) 131(3):528-35, see Applicant's IDS of 7/24/06) in view of Gold et al., Ramsden et al., Blaser et al., and Moses et al.

Matthaeus 1 teach that levels of NGAL protein are upregulated in response to ischemic renal injury in a rat model (see entire selection). By contrast, control animals displayed only minor expression of NGAL, demonstrating that renal injury and repair is associated with an upregulation of NGAL. Such experiments read on the claimed step of "evaluating the renal tubular cell injury status" as recited in claim 30 since given the broadest reasonable interpretation, the investigation and correlation of renal injury status (i.e., control or postischemic subject) with levels of expressed NGAL over time by Matthaeus 1 would be considered to represent "evaluation" of renal injury status.

Similarly, Matthaeus 2 teaches that NGAL protein expression was upregulated after ischemic injury in a rat model of renal ischemia, demonstrating that upregulation of NGAL is

associated with renal injury as well as repair (see entire selection). The reference further teaches that NGAL may play a critical role in the renal response to ischemic injury (last sentence).

The Matthaeus references differ from the claimed invention in that they fail to specifically teach detecting NGAL in **urine** as claimed.

It was well known in the art that disease processes may produce changes in the levels of certain specific analytes, and that measurement of the levels of such analytes can be used to detect the presence of the disease.

As just one example, Gold et al. teach that changes in the levels of certain target molecules (e.g. those not normally found in healthy individuals but known to present in diseased individuals) can be detected in samples from individuals at risk of the disease for the purpose of diagnosis (column 2, line 15 to column 3, line 25).

Therefore, it would have been obvious to one of ordinary skill in the art detect NGAL for the purpose of diagnosing acute renal injury in light of the teachings of Matthaeus 1 or Matthaeus 2 that NGAL is specifically elevated in this disease condition, and further in view of the general knowledge of one skilled in the art that markers changed in response to disease can be used as biomarkers for diagnosis of the disease (as taught for example by Gold et al.).

The Matthaeus 1 and 2 references make clear that the rat studies were performed as an animal model of human disease. Given such a teaching, it would have been obvious to detect NGAL in human subjects for the clear benefit of diagnosing human disease. In such a case, it would have been further obvious to employ urine as the sample source, rather than the kidney tissue samples examined in the rat models of Matthaeus 1 and 2, for the following reasons.

Initially, it is noted that one skilled in the art would immediately recognize that isolation of kidney tissue would be very invasive and therefore unsuitable method for diagnosing renal injury in humans.

Alternative sources of samples for biomarker detection were known in the art; specifically, it was well known to one skilled in the art of biochemical assay at the time of the invention that urine is a non-invasive and easily collected type of sample. See for example Ramsden et al., column 1, lines 15-16, which teaches that urine samples are noninvasive and convenient.

Therefore, in light of the general knowledge of one skilled in the art that urine is an easily collected and non-invasive sample source for assay of biological analytes (as taught for example by Ramsden et al.), it would have been obvious to use urine as the sample source instead of kidney tissue samples when detecting NGAL for diagnosis of renal injury in human subjects, for the advantage of being a non-invasive and easily collected sample.

One would have a reasonable expectation of success because it was known in the prior art that NGAL is excreted in urine, as taught by Blaser et al. and Moses et al.

Blaser et al. teach detection of human neutrophil lipocalin (NGAL) in urine by sandwich ELISA (see in particular the abstract; page 139, section 2.4; and pages 142-143, sections 3.3-3.4).

Moses et al. also teach that NGAL may be detected in human urine by Western Blot (Example 2 and Figure 1B).

As such, in light of the teachings of Blaser et al. and Moses et al., one skilled in the art would have a reasonable expectation of success in using urine as a sample source for detection of

NGAL in response to renal injury (rather than kidney tissue as taught by Matthaeus 1 and 2) since NGAL was known to be excreted in urine.

With respect to the combination of the Matthaeus 1 or 2, Ohlsson et al., Gold et al., Ramsden et al., Blaser et al., and Moses et al. references, it is noted that Ohlsson et al. adds additional evidence that NGAL was known to be elevated in renal injury at the time of the instant invention.

Specifically, Ohlsson et al. teach an ELISA method to detect NGAL (p. 530, left column; p. 531, the section "PR3 versus neutrophil activation and degranulation"; Figures 3-4; and Table 4b in particular). The reference teaches the steps of obtaining a blood plasma sample from a mammalian subject; it would seem that all mammals are "at risk" of developing a renal injury as recited. However, Ohlsson et al. specifically looked at patients with ANCA-associated systemic vasculitis and recorded development of renal failure (p. 529 "Patient material"). The reference further teaches evaluating the renal tubular cell injury status based on the level of NGAL in that Ohlsson et al. teach that ***greatly elevated NGAL levels are strongly correlated with decreased renal function*** (p. 531, the left column, last paragraph). Given the broadest reasonable interpretation of "evaluating the renal tubular cell injury status", the correlating of NGAL levels with renal failure status by Ohlsson et al. meets the limitation.

Taken together with the findings of Matthaeus 1 or 2, it would have been obvious to detect NGAL for the purpose of diagnosing renal dysfunction since the references establish that NGAL is specifically elevated in this disease condition, and further in view of the general knowledge of one skilled in the art that markers changed in response to disease can be used as biomarkers for diagnosis of the disease (as taught for example by Gold et al.).

Although Matthaeus 1, Mattheus 2, and Ohlsson et al. did not examine NGAL levels in urine (Ohlsson et al. employed blood plasma), it would have been obvious to use urine as the sample source instead of the kidney tissue samples when detecting NGAL for diagnosis of renal injury in human subjects, for the advantage of being a non-invasive and easily collected sample (as taught by Ramsden et al.).

One would have a reasonable expectation of success because it was known in the prior art that NGAL is excreted in urine, as taught by Blaser et al. and Moses et al.

With respect to claim 5, as noted above, one would be motivated to detect NGAL in humans for the purpose of diagnosing human disease. One would have a reasonable expectation of success because Matthaeus 1 and 2 clearly indicate that detection of NGAL in rats was done as an animal model, i.e. an animal model of human disease, and further because Ohlsson et al., Moses et al. and Blaser et al. teach that NGAL is also expressed in humans. The Ohlsson et al. reference also establishes that NGAL levels in humans are correlated with renal dysfunction.

With respect to claim 33, it is noted that the claim recites a method "wherein the method **is used to** detect NGAL present in a sample of the first urine output of the subject..." (emphasis added). This language suggests, but does not clearly require, that the urine sample is one that is taken immediately after the onset of renal tubular cell injury. There are no method steps recited in the claim that definitively require that the urine sample assayed as per claim 30 is one which is taken in the first urine output. See MPEP 2111.04. Consequently, the claim language may also be interpreted as merely indicating, for example, one possible application or intended use of the invention, such language is not considered to be limiting and therefore, the references read on the claim.

With respect to claim 53, when taken together with the general knowledge in the art at the time of the invention that ARF can originate from acute renal injury, it would have been further obvious to recognize that subjects suspected of having acute renal tubular cell injury are at risk of ARF.

27. Claims 1, 4, 9-11, 28, 31, 34-36, 39-40, 46-47, 49, and 54-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Matthaeus 1 or Matthaeus 2 in view of Gold et al., Ramsden et al., Blaser et al., and Moses et al., or in the alternative over Matthaeus 1 or Mattheus 2 and Ohlsson et al. in view of Gold et al., Ramsden et al., Blaser et al., and Moses et al. as applied to claims 5, 30, and 32-33 above, and further in view of David et al. (US 4,376,110).

The references are as discussed above. Matthaeus 1, Mattheus 2 and Ohlsson et al. teach that NGAL levels correlate with renal function as discussed in detail above. When taken together with the general knowledge of one skilled in the art that markers changed in response to disease conditions can be used as biomarkers for diagnosis of disease (as taught for example by Gold et al.), it would have been obvious to detect NGAL levels for the purpose of diagnosing renal tubular cell injury, as discussed in detail above. It would have been further obvious to detect NGAL in urine, given that urine is a non-invasive source of sample (as taught by Ramsden et al.) and because NGAL was known to be excreted in urine (as taught by Blaser et al. and Moses et al.).

The instant claims differ in that they relate to antibody-based detection of NGAL, where NGAL is detected by contacting the urine sample with an antibody to NGAL and detecting the antibody-NGAL complex.

However, immunoassays, including those involving a primary "capture" antibody and secondary labeled antibody in a "sandwich" immunoassay format, were well known in the art to be sensitive and rapid means of detecting analytes in samples.

For example, David et al. teach sandwich or "two-site" immunoassays for detecting the presence of analytes in fluids, in which an unlabeled "capture" antibody is bound to a media (solid support) and then contacted with a sample containing the analyte (see in particular the abstract; column 3, line 10 to column 6, line 61, and especially column 4, lines 19-37). After formation of a capture antibody-analyte complex, a second labeled antibody is added which recognizes a different site on the analyte, resulting in the formation of a "sandwich" (see especially column 1, line 47 to column 2, lines 17; column 5, lines 45-60). This type of assay format has great utility in detecting the presence or amount of an analyte, and the improvements reported by David et al. also produce an assay format that is rapid and sensitive while eliminating false positive results (column 8, lines 33-38; and also column 1, line 67 to column 2, line 7).

Therefore, it would have obvious to one of ordinary skill in the art to detect NGAL in the method of Matthaeus 1, Gold et al., Ramsden et al., Blaser et al., and Moses et al., or alternatively in the method of Matthaeus 1, Ohlsson et al., Gold et al., Ramsden et al., Blaser et al., and Moses et al. using the well known sandwich immunoassay format, e.g. as taught by David et al. One would be motivated to employ this method to detect the presence of NGAL

because it is well recognized in the prior art to be a rapid and sensitive method of detecting analytes in a fluid sample.

With respect to claims 10-11, the method of David et al. involves contacting the fluid sample with the media (solid phase) upon which the primary antibody has been immobilized (see for example column 1, lines 47-56; column 6, lines 5-17; and the Example).

With respect to claims 28 and 34-36, Matthaeus 1 teach that NGAL was elevated "after 24 and 48 hours" of ischemia as detected by Western blot. However, it would have been obvious to one of ordinary skill in the art to detect NGAL levels "within 24 hours" out of the normal desire of artisans to improve upon what is already known. See MPEP 2144.05.

In particular, one would be motivated to detect NGAL within 24 hours or earlier in order to diagnose disease earlier, and therefore to allow for timely interventions to be performed. One would have a reasonable expectation of success because the immunoassay method of David et al. is more sensitive, such that upregulation of NGAL would be reasonably expected to be detectable at earlier time points than by Western blot (as performed by Matthaeus 1).

In addition, it would have been obvious to employ a sample size of "up to 1 milliliter" as in claim 28 given that sample size was recognized in the prior art as a result-effective variable, for example when employing test strip devices for detecting analytes. As such, it would have been a matter of routine optimization to select a suitable volume of urine for assay within the claimed range.

With respect to claim 40, Matthaeus 1 teach comparison of NGAL levels in control and disease subjects and reported that only minor expression of NGAL was seen in control animals

(see right column). The minor expression levels of NGAL would therefore be considered to distinguish the subjects with the renal tubular cell injury from those without.

Regarding claims 47, and 55 which recites that the level of antibody-NGAL complex correlates with the extent of injury, it is noted that while the claim might suggest additional steps, none are recited or clearly required by the claim. Claim scope is not limited by such language (see MPEP 2111.04). Accordingly, the reference teachings read on the claims since this statement may be interpreted (for example) as simply describing properties of NGAL and does not require additional steps or elements.

Similarly, with respect to claim 54, which recites that the method is "used to" predict ARF, this limitation does not clearly require any additional method steps or elements. As such, this limitation may be reasonably interpreted as referring to a possible intended use of the method and does not limit the claim scope.

With respect to claims 49 and 56, when taken together with the general knowledge in the art at the time of the invention that ARF can originate from acute renal injury, it would have been further obvious to recognize that subjects suspected of having acute renal tubular cell injury are at risk of ARF.

28. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Matthaeus 1 in view of Gold et al., Ramsden et al., Blaser et al., and Moses et al., or in the alternative over Matthaeus 1 and Ohlsson et al. in view of Gold et al., Ramsden et al., Blaser et al., and Moses et al. as applied to claim 30 above, and further in view of Valkirs et al. (US 2003/0109420 A1).

The references are as discussed above, which teach a method for detecting NGAL in a urine sample substantially as claimed, but which fail to specifically teach that the urine sample comprises a plurality of urine samples that are obtained intermittently or continuously.

Valkirs et al. teach that one skilled in the art would recognize the value of testing multiple samples (for example, a series of samples obtained at successive time points) from the same individual, e.g. in allowing identification of changes in levels of markers over time [0107]. Such data can provide information about disease status, including appropriateness about drug therapies and identification of patient outcome.

29. Claims 2-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matthaeus 1 in view of Gold et al., Ramsden et al., Blaser et al., and Moses et al., or in the alternative over Matthaeus 1 and Ohlsson et al. in view of Gold et al., Ramsden et al., Blaser et al., and Moses et al., as applied to claim 30 above, and further in view of Linzer et al. (US 3,635,091)

The references are as discussed above, which teach a method for detecting NGAL in a urine sample substantially as claimed, but which fail to specifically teach that the urine sample comprises a plurality of urine samples that are obtained continuously.

Linzer et al. teach a urine sample collector in which urine obtained by having the patient urinate continuously into the container (see especially column 1, lines 1-45 and column 2, lines 46-57). The collector separates the urine into two fractions, so that if necessary the initial urine fraction can be compared with the midstream specimen (column 2, lines 46-57). The collector can also be adapted so that the liquid can be deposited into multiple independent containers (the

abstract). The reference teaches that the sample collector has the advantage in that it provides a specimen free of contamination (column 1, lines 1-73).

Therefore, it would have been obvious to obtain multiple urine samples in a continuous fashion (continuous stream of urine) using the urine specimen collector of Linzer et al. in order to ensure that the analyzed sample was free of contamination.

30. Claims 33-38 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matthaeus 1 in view of Gold et al., Ramsden et al., Blaser et al., and Moses et al., or in the alternative over Matthaeus 1 and Ohlsson et al. in view of Gold et al., Ramsden et al., Blaser et al., and Moses et al. as applied to claim 30 above, and further in view of Muramutsu (Kidney International, Vol. 62 (2002), pages 1601-1610, Applicant's IDS of 10/18/04).

The references are as discussed above. Matthaeus 1 teach that NGAL was elevated "after 24 and 48 hours" of renal ischemia. However, the references fail to specifically teach detection of NGAL in relation to one of the specific events recited in claims 37-38 and 59. As also discussed above, however, the references fail to specifically teach detection of NGAL "within 24 hours" or at the specified times recited in claim 35.

Muramutsu et al. teach that it is imperative to diagnose acute renal failure (ARF) as soon as possible, and that disease markers that can be measured in blood or urine would be of extreme value since ARF is associated with high morbidity and mortality (see especially page 1601).

In particular, the reference teaches screening for a biomarker of ARF (Cyr61) by detecting the presence of urinary Cyr61 within specified times in relation to the onset of induced renal ischemia, as a model of ARF (see especially pages 1603-1604, "Urine Collection"; page

1606; and Figure 8). The reference exemplifies time points of 3-6, 6-9, 9-12, 12-18, and 18-24 hours after ischemia (see especially the legend to Figure 8) and report that the levels of urinary Cyr61 were seen to increase within 3-6 hours (page 1608). The reference also teaches that no urine was produced within the first three hours, such that the first time point of 3-6 hours would represent the first urine output (legend to Figure 8).

Therefore, with respect to claims 33-36, it would have been obvious to one of ordinary skill in the art to detect NGAL levels as early as possible as taught by Muramatsu, and in particular within the recited time ranges in relation to the onset of injury out of the normal desire of artisans to improve upon what is already known. See MPEP 2144.05. In particular, one would be motivated to detect NGAL within 24 hours or earlier in order to diagnose disease earlier, and therefore to allow for timely interventions to be performed. Given that Muramatsu exemplify time points that overlap those disclosed (e.g., 3-6 hours), it would have been a matter of routine optimization to determine and select appropriate times for urine collection based on when NGAL is increased.

With respect to claims 37-38 and 59, Muramatsu et al. further teach that the biomarker Cyr61 is rapidly induced in the kidney in response to renal ischemia, and that because of this rapid induction pattern, it may serve as an early disease marker for renal injury (see the paragraph bridging pages 1608-1609). The reference further indicates that the marker could be used in a variety of settings including after contrast administration, chemotherapy, transplantation, vascular surgery, or in kidney donors, or with multi-organ failure in the ICU.

One skilled in the art would clearly appreciate the parallels between the biomarker Cyr61 as taught by Muramatsu and the NGAL protein taught by Matthaeus 1 (and also by Ohlssen et

al.). Matthaeus 1 teach that like Cyr61, NGAL is upregulated in response to renal ischemia. Taken together with the teachings of Muramutsu et al. that a marker exhibiting this property may serve as an early disease marker for renal injury after transplantation or vascular surgery, one skilled in the art would be highly motivated to employ NGAL as a biomarker of renal tubular cell injury for this same purpose. For example, it would have been obvious to detect NGAL in the context of transplantation or vascular surgery for the purpose of diagnosing ARF.

With respect to claim 38, it would be immediately envisaged that such significant medical events as kidney transplantation or vascular surgery would involve admission to an intensive care unit.

31. Claims 47-48 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matthaeus 1 or Matthaeus 2 in view of Gold et al., Ramsden et al., Blaser et al., Moses et al., and David et al. or in the alternative over Matthaeus 1 or Mattheus 2 and Ohlsson et al. in view of Gold et al., Ramsden et al., Blaser et al., Moses et al., and David et al. as applied to claims 1, 31, and 46 above, and further in view of Kosako et al. (US 5,527,714).

The references discussed above fail to specifically teach the step of correlating the level of antibody-NGAL complex to the extent of the acute renal tubular cell injury.

Kosako et al. teaches antigen/antibody reactions to prepare an analyte for diagnosis, in which the level of antigen/antibody complex as measured using a detectable marker is measured. The amount of marker that is bound to the analyte (antigen) directly correlates with the amount of analyte in the sample and *becomes an index of the presence or extent of a disease* (column 1, lines 18-28).

The teachings of Kosako et al. establish that it was known to use markers of disease not only to indicate the presence of a disease but also its extent or severity.

Therefore, when taken together with the teachings of Matthaeus 1 or Matthaeus 2 which establish NGAL as a marker of acute ischemic renal injury, it would have been further obvious to one of ordinary skill in the art to correlate NGAL levels not only with the presence of disease but with the extent or severity of disease.

32. Claim 51 is rejected under 35 U.S.C. 103(a) as being unpatentable over Matthaeus 1 or Matthaeus 2 in view of Gold et al., Ramsden et al., Blaser et al., and Moses et al., or in the alternative over either Matthaeus 1 or Matthaeus 2 and Ohlsson et al. in view of Gold et al., Ramsden et al., Blaser et al., and Moses et al. (as applied to claim 30 above), and further in view of and Madsen et al. (US 4,357,343) and Calvet et al. (US 5,552,313).

The references discussed above fail to specifically teach determining the presence of an acute renal tubular cell injury that is an *acute nephrotoxic injury.* In particular, Matthaeus 1 and 2 relate to renal injury caused by acute ischemia rather than nephrotoxicity.

Madsen et al. teach that nephrotoxic injury can result from excessive exposure to drugs, chemicals, heavy metals, etc. that are toxic to the renal tubule cells; and further that nephrotoxic injury, together with renal ischemia, constitute two categories of possible causes of acute renal failure (column 1, lines 23-30). Calvet et al. teach that nephrotoxic injury causes kidney tubule damage and necrosis, followed by repair of the damage and regeneration of normal renal function (column 1, lines 54-56).

When taken together with the teachings of Matthaeus 1 or Matthaeus 2 that NGAL is involved in renal injury and repair, it would have been further obvious to one of ordinary skill in the art to employ NGAL as a marker of renal injury caused by acute nephrotoxic injury (such as excessive exposure to heavy metals as taught by Madsen et al.). In particular, given that both ischemic injury and nephrotoxic injury were recognized in the art as being causes of acute renal failure (as taught by Madsen et al.), it would have been obvious to employ NGAL as a marker of renal injury caused by nephrotoxic as well as ischemic origin.

One of ordinary skill in the art would have had a reasonable expectation of success because Calvet et al. teaches that nephrotoxic injury is followed by repair; and the teachings of Matthaeus 1 and Matthaeus 2 indicate that NGAL may play a critical role in the renal response to injury (see, e.g., Matthaeus 1 at the last sentence).

33. Claim 52 is rejected under 35 U.S.C. 103(a) as being unpatentable over Matthaeus 1 or Matthaeus 2 in view of Gold et al., Ramsden et al., Blaser et al., and Moses et al., or in the alternative over either Matthaeus 1 or Matthaeus 2 and Ohlsson et al. in view of Gold et al., Ramsden et al., Blaser et al., and Moses et al. (as applied to claim 30 above), and further in view of Brady et al. (US 2002/0048779 A1).

The references discussed above fail to specify whether urine is "unprocessed" or not. Brady et al. teach assaying of biological materials including urine from a subject, in which the biological materials may be unprocessed or processed [0082].

Therefore, given that it was known to assay unprocessed urine, it would have been further obvious to one of ordinary skill in the art to provide the urine sample in unprocessed form.

Motivation to use unprocessed urine would be found in the general knowledge of one skilled in the art that fewer processing steps would result in a faster, simpler method.

Double Patenting

34. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

35. Claims 1-5, 9-11, 28, 30-40, 46-56, and 59 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2, 4, 7-10, and 22-39 of copending Application No. 11/096,113 in view of Ramsden et al., Blaser et al., and Moses et al.

Copending application No. 11/096,113 recites a method for evaluation of a renal tubular cell injury in a mammalian subject (see especially claims 27 and 31) based on the level of NGAL

in a sample. The level of NGAL may be determined by antibody binding (see claim 2), as recited in instant claim 1, for example.

The claims of the copending application differ from the instantly claimed invention in that in application No. 11/096,113 the sample assayed for NGAL is *blood or serum* (see claims 2, 9, and 24 in particular), while the sample assayed in the instant invention is *urine.*

However, it was well known to one skilled in the art of biochemical assay at the time of the invention that urine is a non-invasive and easily collected type of sample. See for example Ramsden et al., column 1, lines 15-16, which teaches that urine samples are noninvasive and convenient. In addition, it was known in the prior art that NGAL is excreted in urine: Blaser et al. teach detection of human neutrophil lipocalin (NGAL) in urine by sandwich ELISA (see in particular the abstract; page 139, section 2.4; and pages 142-143, sections 3.3-3.4). Moses et al. also teach that NGAL may be detected in human urine by Western Blot (Example 2 and Figure 1B).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to detect NGAL in urine rather than in blood or serum for the advantages of ease of collection associated with the non-invasive nature of urine sampling, as taught by Ramsden et al. In light of the teachings of Blaser et al. and Moses et al., one skilled in the art would have a reasonable expectation of success in using urine as a sample source for detection of NGAL in response to renal injury since NGAL was also known to be excreted in urine.

This is a provisional obviousness-type double patenting rejection.

36. Claims 1-5, 9-11, 28, 30-40, 46-56, and 59 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 30-31, 33-45, and 47-50 of copending Application No. 11/770,422 in view of David et al.

Copending Application No. 11/770,422 recites a method of diagnosing renal disorder by providing a sample of body fluid from a subject (which may be urine) and detecting the concentration of NGAL in the sample (see especially claims 30 and 45). The renal disorder may be an acute renal tubular cell injury such as acute renal failure, acute tubular necrosis, or acute tubulo-interstitial nephropathy (see claim 40). The renal injury may also be caused by a nephrotoxic agent (claim 41).

The copending application differs from the instant claims in that although it recites that NGAL can be measured by means of a specific binding molecule (claim 44), it does not specify antigen-antibody binding.

However, immunoassays involving antibodies, including those involving a primary "capture" antibody and secondary labeled antibody in a "sandwich" immunoassay format, were well known in the art to be sensitive and rapid means of detecting analytes in samples.

For example, David et al. teach sandwich or "two-site" immunoassays for detecting the presence of analytes in fluids, in which an unlabeled "capture" antibody is bound to a media (solid support) and then contacted with a sample containing the analyte (see in particular the abstract; column 3, line 10 to column 6, line 61, and especially column 4, lines 19-37). After formation of a capture antibody-analyte complex, a second labeled antibody is added which recognizes a different site on the analyte, resulting in the formation of a "sandwich" (see especially column 1, line 47 to column 2, lines 17; column 5, lines 45-60). This type of assay

format has great utility in detecting the presence or amount of an analyte, and the improvements reported by David et al. also produce an assay format that is rapid and sensitive while eliminating false positive results (column 8, lines 33-38; and also column 1, line 67 to column 2, line 7).

Therefore, it would have obvious to one of ordinary skill in the art to detect NGAL in the method of the '422 application by the well known two-antibody sandwich immunoassay format, e.g. as taught by David et al. One would be motivated to employ this method to detect the presence of NGAL because it is well recognized in the prior art to be a rapid and sensitive method of detecting analytes in a fluid sample.

37. Claims 1-5, 9-11, 28, 30-40, 46-56, and 59 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 22, 24-36, 38-42 and 44 of copending Application No. 11/770,372 in view of David et al., Ramsden et al., Blaser et al., and Moses et al.

The '372 application recites a method of diagnosing a renal disorder in a subject based on concentrations of NGAL in a body fluid sample (see especially claims 22 and 44). The renal disorder may be an acute renal tubular cell injury such as acute renal failure, acute tubular necrosis or acute tubulo-interstitial nephropathy (claim 32) and may be caused by a nephrotoxic agent (see claim 33).

The '372 application does not recite that NGAL is detected by antibody-NGAL complex formation. However, in light of the teachings of David et al., it would have been obvious to detect NGAL by means of a two-antibody sandwich immunoassay as discussed above.

The '372 application also fails to recite that the body sample assayed is urine.

However, in light of the teachings of Ramsden et al., Blaser et al. and Moses et al. discussed above, it would have been obvious to one of ordinary skill in the art at the time of the invention to detect NGAL in urine rather than in blood or serum (as in the '372 application) with a reasonable expectation of success.

38. Claims 1-5, 9-11, 28, 30-40, 46-56, and 59 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 29-30, 32-44, and 46-49 of copending Application No. 11/770,214 in view of David et al.

The '214 application recites a method of diagnosing renal disorder in humans by determining the concentration of NGAL in a body fluid sample (which may be urine) (see especially claims 29 and 44). The renal disorder may be an acute renal tubular cell injury such as acute renal failure, acute tubular necrosis or acute tubulo-interstitial nephropathy (claim 39) and may be caused by a nephrotoxic agent (see claim 40).

The copending application differs from the instant claims in that although it recites that NGAL can be measured by means of a specific binding molecule (claim 43), it does not specify antigen-antibody binding.

The '214 application does not recite that NGAL is detected by antibody-NGAL complex formation. However, in light of the teachings of David et al., it would have been obvious to detect NGAL by means of a two-antibody sandwich immunoassay as discussed above.

39. Claims 1-5, 9-11, 28, 30-40, 46-56, and 59 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 29, 31-43, and 45-49 of copending Application No. 11/770,245 in view David et al., Ramsden et al., Blaser et al., and Moses et al.

The '245 application recites a method of diagnosing renal disorder in humans by determining the concentration of NGAL in a body fluid sample (see especially claim 29).

The copending application differs from the instant claims in that although it recites that NGAL can be measured by means of a specific binding molecule (claim 43), it does not specify antigen-antibody binding. The renal disorder may be an acute renal tubular cell injury such as acute renal failure, acute tubular necrosis or acute tubulo-interstitial nephropathy (claim 39) and may be caused by a nephrotoxic agent (see claim 40).

The '245 application does not recite that NGAL is detected by antibody-NGAL complex formation. However, in light of the teachings of David et al., it would have been obvious to detect NGAL by means of a two-antibody sandwich immunoassay as discussed above.

The '245 application also fails to recite that the body sample assayed is urine.

However, in light of the teachings of Ramsden et al., Blaser et al. and Moses et al. discussed above, it would have been obvious to one of ordinary skill in the art at the time of the invention to detect NGAL in urine rather than in blood or serum (as in the '245 application) with a reasonable expectation of success.

Response to Arguments

40. Applicant's arguments filed 11/13/07 have been fully considered.

41. With respect to *Priority,* it is noted that this issue does not appear to be currently material to patentability as all of the art relied upon above was publicly available prior to the earliest claimed effective filing date. However, Applicant's arguments are addressed below.

Applicant argues that the provisional applications meet the requirements of 119(e) and refers to the decision in *New Railhead Mf., L.L.C. v. Vermeer Mfg. Co.* in which the district court assumed that a patent at issue was entitled to the priority date of the provisional application (Applicant's Reply, pages 20-21). This is not found persuasive because the facts of that case clearly differ and no clear general conclusions by the court are made that would allow parallels to be drawn here. The brief statement in the decision that the lower court "assumed" entitlement to an earlier filing date is not seen as a broad controlling statement that would warrant a different interpretation of the provisions of 35 U.S.C. 112 in the instant case.

Applicant further argues that the provisional application fully supports at least one pre-amended claim (Reply, pages 21-22), which is not on point since it is the instant claims as amended which must be evaluated as to effective filing date, on a claim-by-claim basis.

Furthermore, the passages indicated by Applicant have been considered but are not found to support NGAL as a nephrotoxic marker as asserted. The mention of nephrotoxicity at page 1 is in the context of "guid[ing] pharmaceutical development" and not in the context of determining or diagnosing the presence of injury as in the instant claims. Although page 12 refers to "administration of pharmaceuticals, radiocontrast dyes, or other medicament substances", the specification does not identify such substances as being nephrotoxic. Not all pharmaceuticals, etc. are necessarily nephrotoxic; thus, no inherent support can be seen in the '143 provisional application for determination of acute nephrotoxic injury as argued by

Applicant. In addition, the instant claims are also now directed to determining the presence of *acute* renal injury. No description of methods of determining *acute nephrotoxic injury* could be found in the provisional application.

Finally, the instant claims are not limited to ischemic and nephrotoxic injury *only*, but rather are directed to any type of acute renal tubular cell injury, which is broader in scope.

Rejections under § 112

42. With respect to the rejection of claim 40 under § 112, 1st paragraph as containing new matter, Applicant's arguments (see pages 27-28) have been fully considered but are not persuasive of error. Applicant points to paragraph 100 of the specification as providing support for the claimed subject matter. This is not found persuasive because for the reasons detailed above in the body of the rejection, claim 40 is broader in scope than the subject matter described in paragraph 100, which relates to the results of a specific example and does not provide support for the subject matter now claimed generically. The claim fails to incorporate relevant limitations disclosed in paragraph 100 (i.e., that NGAL levels of >100 ng/ml being associated with the acute renal tubular cell injury of cadaveric kidney transplant rejection, etc.). The specification does not clearly introduce the general concept of NGAL levels that distinguish acute renal tubular cell injury from those that do not have this type of injury. Given the diversity of renal injuries that would be encompassed by the claims, one skilled in the art would not know based on the specification what NGAL level(s) might discriminate healthy vs. disease subjects for other types of acute renal injuries besides cadaveric kidney transplant rejection. Threshold levels for NGAL in various injuries were also apparently not known in the art at the time of the invention. For

these reasons, it is maintained that the claimed subject matter broadens the scope of the original disclosure and therefore fails to meet the written description requirement. See MPEP 2163.05

43. With respect to the rejection of claim 37 under § 112, 1st paragraph as containing new matter, Applicant's argues that the term "cardiovascular surgery" and "onset of" have been deleted from the claim, and that one skilled in the art would understand that such events as stroke, trauma, sepsis and dehydration can cause acute renal tubular cell injury (Reply, page 29).

The Examiner notes that claim 37 depends from claims 35 and 36, which require obtaining urine samples at specified periods of time in relation to renal injury. Although the specification mentions the conditions of stroke, trauma, sepsis and dehydration at [0038], this disclosure conveys only that the method could be used in subjects with these disease conditions. Although stroke and trauma could arguably be thought of as discrete events in time, sepsis and dehydration refer to pathophysiologies that would span continuums of severity. It is unclear how they would be considered "events". Therefore, while the specification does convey evidence of possession of methods of determining renal injury in patients with sepsis or dehydration, there is nothing that would indicate that these disease conditions are to be considered discrete "events" in time in relation to which urine is sampled. Given that the claims specifically relate to sampling in relation to such events, and because the specification does not indicate how these disease conditions would constitute "events", it is maintained that the disclosure fails to convey evidence of possession of the claimed subject matter. The skilled artisan would not know, based on the specification, whether urine samples would be taken from onset of these conditions, clinical diagnosis, etc.

It is noted that claim 37 was also rejected as reciting "coronary bypass surgery" as this term could not be found in the specification. Applicant's Reply does not apparently include arguments regarding this aspect of the rejection.

44. With respect to the rejection of claim 40 under § 112, 2nd paragraph, Applicant argues that the examples in the specification at paragraphs 100-101 provide an express description of the claimed invention; that the level of skill in the art is high; and that guided by the teaching of the specification one skilled in the art could a particular level of NGAL without undue experimentation (Reply, pages 31-32). Applicant's arguments are not found persuasive because they appear to be directed to issues of enablement rather than definiteness of claim language.

Rejections under § 103(a)

45. With respect to the rejections of claims 5, 30, and 32-33, Applicant's arguments have been fully considered but are not persuasive. Applicant argues that Matthaeus 1 does not discuss, demonstrate or suggest sampling of the *urine*, instead sampling kidney tissue (Reply, page 36). In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, it is acknowledged that Matthaeus 1 does not teach urine; rather, the Ramsden et al., Blaser et al., and Moses et al. references have been relied upon for this teaching.

46. Applicant further argues that Mattheus 1 does not address immediate or early detection of acute renal injury at times less than 24 hours after the ischemic event and does not mention renal

injuries caused by toxins (Reply, pages 37). Such arguments are not commensurate with the scope of the instant claims. See for example claim 1, in which the renal injury may be caused either by nephrotoxic means or by ischemic injury (as in Matthaeus 1), and which recites no limitations as to early detection less than 24 hours after the ischemic event.

Applicant further argues that it is well known to persons of ordinary skill in the art that the proximal tubules remove, rather than express, a protein from the blood (Reply, page 37). The Examiner surmises this line of argument to indicate that one of ordinary skill in the art would not reasonably expect success in finding NGAL in the *urine* based on the experiments of Matthaeus 1, where NGAL was observed by immunohistochemical staining of kidney tissue.

Applicant points to the accompanying Declaration under 35 USC 1.132 of Dr. Barasch, asserted to establish that it is known that NGAL protein appearing in the proximal tubules does not pass into the urine.

The Declaration under 37 CFR 1.132 filed 11/13/07 is insufficient to overcome the rejection of the claims under § 103(a) based upon the Matthaeus 1 reference as set forth in the last Office action because:

The Barasch Declaration refers to the results of an experiment published as Mori et al. in March 2005 (see Declaration, item 5). However, the focus when making a determination of obviousness should be on what a person of ordinary skill in the pertinent art would have known **at the time of the invention**, and on what such a person would have reasonably expected to have been able to do in view of that knowledge. MPEP 2141, emphasis added. The Mori et al. publication referred to the Declaration was published after the filing date of the instant application. Therefore, it cannot speak to the knowledge in the art at the time of the invention

and fails to provide evidence to establish that it was well known in the art at the time of the invention that proteins expressed in proximal tubule cells would be removed and not released into urine.

For these reasons, even if the NGAL protein detected by Matthaeus 1 corresponded to a separate pool of NGAL that would not be released into the urine as apparently argued by Applicant, one of ordinary skill in the art *at the time of the invention* would not be aware of this fact. Therefore, it is maintained for reasons of record that one of ordinary skill in the art would reasonably expect success in detecting NGAL in urine based on the teachings of the references.

47. Applicant further argues that Matthaeus 1 mentions an ischemic event but does not explain the type, extent and duration of the ischemic event (reply, page 37). Such remarks fail to point out how the language of the claims distinguishes them over the references. Claim 1 (for example) does not require any particular type, extent, or duration of ischemic event.

48. Applicant further argues that Matthaeus 1 teaches that complexes of NGAL and MMP and/or TMP-1 are upregulated (Reply, page 37). The Examiner disagrees. Although Matthaeus 1 states that NGAL "has been shown to occur in disulfide-linked complexes", the results of the experiments are clearly taught as indicating that "NGAL protein expression was upregulated".

49. Applicant further argues that Matthaeus 1 does not teach sampling of any body fluid within 24 hours of a renal injury. However, absent evidence of criticality it is maintained that it would have been obvious to sample "within 24 hours" out of the course of routine optimization with a reasonable expectation of success given that Matthaeus 1 teach that NGAL was upregulated "after 24 and 48 hours".

50. Applicant further argues that since Matthaeus 1 studied gene expression in body tissue, the methods involving kidney tissue taught therein were particularly suited to this question such that it would not have been obvious to modify the reference teachings (Reply, page 38). This is not found persuasive because Matthaeus 1 studied NGAL protein expression as well as gene expression. Therefore, arguments that the sample type was particularly suited to study of gene expression are not persuasive since the studies extended beyond this specific goal.

In addition, it is clear that Matthaeus 1 conducted experiments in a rat model of disease (this is made explicit in Matthaeus 2, who refer to a "rat model of renal ischemia"). For example, Matthaeus 1 state that the purpose of their experiment is to "further elucidate the processes involved in renal injury and repair". The findings reported therein support a "critical role in the renal response to injury" for NGAL. It is therefore maintained for reasons of record that one of ordinary skill in the art would find it obvious to detect NGAL in human subjects for the clear benefit of diagnosing human disease, and then when doing so, it would have been obvious to choose urine as a less invasive sample source than actual kidney tissue.

For all of these reasons, it is maintained that the evidence of non-obviousness fails to outweigh the evidence of obviousness.

51. With respect to the rejections of claims 1, 4, 9-11, 28, 31, 34-36, 39-40 and 46, Applicant's arguments have been fully considered but are not persuasive. Applicant argues that the claimed ranges are "within 24 hours", i.e. less than 24 hours, while Matthaeus et al. teaches "after 24 and 48 hours" (Reply, page 39). It is noted that such arguments are not commensurate with the scope of the rejected claims, which are not limited to detection "within 24 hours". Furthermore, the disclosure of each reference must be evaluated for what it fairly teaches one of

ordinary skill in the art, including not only the specific teachings, but also the inferences which one of ordinary skill in the art would reasonably have been expected to draw therefrom. See In re Boe, 355 F.2d 961, 965, 148 USPQ 507, 510 (CCPA 1966); and In re Preda, 401 F.2d 825, 826-27, 159 USPQ 342, 344 (CCPA 1968).

In the instant case, it is maintained for reasons of record the person of ordinary skill in the art would have found it obvious to try to detect NGAL as early as possible in order to diagnose disease earlier out of the course of routine optimization.

In this regard, Applicant further argues that Matthaeus 1 is not concerned with "diagnosing disease" but with repair of injury, such that the identified motivation to diagnose disease earlier is not applicable (Reply, paragraph bridging pages 39-40). This is not found persuasive because as stated in the recent decision in KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1741, 82 USPQ2d 1385, 1397 (2007), "In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls. What matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under § 103." Furthermore, the instant rejection is not based solely on Matthaeus 1 but also takes into account the general knowledge of the skilled artisan that markers changed in response to disease can be used as biomarkers for diagnosis of the disease (as taught for example by Gold et al.). Therefore, even if Matthaeus 1 does not have the same purpose or motivation as Applicants, it is maintained for reasons of record that one of ordinary skilled in the art would find the teachings therein that NGAL is upregulated in response to renal injury to have diagnostic implications.

Applicant further argues that it would have been technically feasible for Matthaeus 1 to excise kidney samples at any time prior to 24 hours (Reply, page 40). The Examiner concedes this point but does not see how this would tend to indicate that one skilled in the art would not reasonably expect success in using the known immunoassay methods of David et al., rather than the Western blot assay of Matthaeus 1, to detect NGAL.

52. With respect to the rejection of claim 2, Applicant argues that Valkirs relates to acute coronary syndrome and does not appear to be particularly relevant to Applicant's claimed invention (Reply, page 41).

This is not found persuasive because the test for obviousness involves consideration of what the combined teachings, as opposed to the individual teachings, of the references would have suggested to those of ordinary skill in the art. In re Young, 927 F.2d 588, 591, 18 USPQ2d 1089, 1091 (Fed. Cir. 1991); In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). In the instant case, although Valkirs focused on acute coronary syndrome, it is maintained that a person of ordinary skill in the art of clinical assay would find it obvious to extend the teachings regarding the value of testing multiple samples from the same individual to other diseases.

53. With respect to the rejections of claims 2-3, Applicant argues (Reply, page 42) that Linzer is not particularly relevant to Applicant's claimed invention. This is not found persuasive because Linzer relates to a device for collecting urine samples from a patient, which is particularly relevant to the method of the noted references in which urine samples are assayed.

54. With respect to the rejections of claims 33-38, Applicant argues that the Muramutsu reference is not particularly relevant to Applicant's claimed invention (Reply, page 43).

Muramutsu et al. teach that it is imperative to diagnose acute renal failure as soon as possible, and exemplifies assaying for other known markers in relation to the time of onset of renal ischemia. This is relevant to the claimed invention because it indicates that one of ordinary skill in the art would have been highly motivated to assay for newly discovered markers of renal injury as soon as possible after injury.

Double Patenting

55. With respect to the rejections over copending Application No. 11/096,113, Applicant argues that NGAL in the blood and NGAL in urine are from distinct sources and represent separate and distinct pools of NAL (Reply, pages 44-45). Applicant refers to an affidavit or declaration filed in the prior application in support of such remarks. This is not found persuasive because affidavits or declarations, such as those submitted under 37 CFR 1.130, 1.131, and 1.132, filed during the prosecution of the prior application do not automatically become a part of this application. Where it is desired to rely on an earlier filed affidavit or declaration, the applicant should make the remarks of record in this application and include a copy of the original affidavit or declaration filed in the prior application.

Conclusion

56. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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